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EXAMINER	
HUYNH, PHUONG N	
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/046,922	ALITALO ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 12-13, 21-33, 35-36 and 38-76* is/are pending in the application.

4a) Of the above claim(s) *39-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 12-13, 21-33, 35-36, 38 and 75-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4, 12-13, 21-33, 35-36 and 38-76 are pending.

2. Claims 39-74 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 1/17/06, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 12-13, 21-33, 35-36, 38 and 75-76 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue, (2) the said isolated peptide wherein the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) further comprises amino- and carboxy-terminal cysteine residues that forms an intramolecular bond between said cysteine amino acid residues to form a cyclic peptide, (3) the isolated peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes CGYWLTIWGC (SEQ ID NO: 35), (4) An isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), and WFSASLRFR (SEQ ID NO: 43) and wherein the peptide inhibits human Vascular Endothelial Growth Factor C (VEGFR-C) binding to human VEGFR-3, (4) A chimeric protein comprising the isolated peptide

with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue and a therapeutic protein, (5) the chimeric protein mentioned above wherein the therapeutic protein is a tumor necrosis factor, an antibody or an Fc fragment thereof, (6) A peptide dimer comprising first and second peptide wherein the first and second peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue, (6) a composition comprising the isolated peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue, (7) a label peptide comprising the isolated peptide with an amino acid sequence consisting of 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes eight amino acids satisfying the formula: $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID N0: 32), wherein the amino acid residue at X_1 is glycine residue, the amino acid residue at X_2 is tyrosine residue, the amino acid residue at X_3 is tryptophan residue, the amino acid residue at X_4 is leucine residue, the amino acid residue at X_5 is threonine residue, the amino acid residue at X_6 is isoleucine residue, and the amino acid residue at X_8 is glycine residue and a label, and (8) the label peptide mentioned above wherein the label is selected from the group consisting of a radionuclide, a dye, an enzyme, and an enzyme substrate for detection or binding assays, **does not** reasonably provide enablement for any isolated peptide as set forth in claims 1-4, 12-13,

21-33, 35-36, 38 and 75 for treating any disease such as cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

A. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X1 through X8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8.

In order to make and use of the claimed invention, one has to be in possession of the peptide sequence and be able to binds human VEGFR-3.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide GYWLTIWG further comprises amino and carboxy terminal

cysteine residues to form a cyclic peptide via an intramolecular bond between said cysteine residues. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or screening assays. There is a lack of guidance as to the structure of peptide with an amino acid sequence consisting of 8-100 amino acids wherein the amino acid sequence "includes" eight amino acids satisfying the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) wherein X1 through X8 are any conservative amino acid substitution without the amino acid sequence. The term "includes" or "including" as defined by the specification to mean "comprising", which is open-ended. There is insufficient guidance as to which amino acids to be added in addition to any conservative amino acid substitution such that the resulting peptide still binds to human VEGFR-3. There is no disclosure of the claimed peptide longer than 8-100 amino acids in length that binds to human VEGFR-3. Further, there is insufficient guidance as to which three amino acids within $X_1X_2X_3X_4X_5X_6X_7X_8$ of a peptide 8-100 in length to be substitute for which conservative amino acids such that the peptide maintains its three dimensional structure and still binds to human VEGFR-3. Even assuming the 8-mer peptide is the common attribute necessary for receptor binding, there are no working examples of such peptide having 63% identity with GYWLTIWG (3 amino acids substitution out of 8 amino acids) still binds to human VEGFR-3, let alone a peptide having 100 amino acids in length and merely 5% sequence identity to GYWLTIWG. The state of the art with respect to the specificity of receptor binding by VEGF-D is different in mouse and man. For example, it is known that human VEGF-D binds to VEGFR-2 and VEGFR-3. Unlike human VEGF-D that binds to both VEGFR-2 and VEGFR-3, mouse VEGF-D is specific for VEGFR-3 in the mouse, mouse VEGF-D does not bind mouse VEGFR-2 (see Baldwin et al, J Biol Chem 276(22): 19166-19171, 2001; PTO 892). The specification provides no guidance on this point. Further, the specification discloses the cysteine residues are added at the N and Carboxy-terminal end of the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ where X_1 is G, X_2 is Y, X_3 is W, X_4 is L, X_5 is T, X_6 is I, X_7 is W and X_8 is G, not at the N and C-terminal ends of the isolated peptide that is 100, 99, 98, ...25 etc amino acids in length, see specification at page 28. The specification does not teach how to make any peptides mentioned above that mimicked a discontinuous binding site.

Clearly, any peptide with an amino acid sequence consisting of 8-100 amino acids in length and having any 3 conservative amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no

resemblance to CGYWLTIWGC is clearly not enabled. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention.

B. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 8-100 amino acids in length, wherein the peptide binds to human VEGFR-3 and comprising the sequence Y_1GYWLTIWGY_2 (SEQ ID NO: 34), wherein Y_1 and Y_2 are any amino acids.

In order to make and use of the claimed invention, one has to be in possession of the peptide and be able to binds human VEGFR-3.

In addition to the problem of the structure of peptide with an amino acid sequence consisting of 8-100 amino acids without the amino acid sequence, and binds to human VEGFR-3, there is insufficient guidance as to the amino acids to be substitute at position Y_1 and Y_2 and 8-100 amino acids in length. There is not a single peptide such as 100 amino acids in length that includes the any conservative substitution at any three amino acids in $X_1X_2X_3X_4X_5X_6X_7X_8$ and still binds to human VEGF receptor. Other than cysteines residues at position Y_1 and Y_2, the specification does not teach which amino acids to be substituted and still maintains its cyclic structure and binding to human VEGFR-3. Further, the term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is a lack of guidance as to such amino acids other than cysteine for Y_1 and Y_2 in Y_1GYWLTIWGY_2. There are no working examples of such peptide binding to human VEGFR-3. The specification does not teach any assays that are useful for screening variants and is predictive of success in vivo for treating any disease such as ischemia, lymph edema, restenosis and cancer. The state of the art is that even a single amino acid change in a protein can lead to unpredictable changes in the biological activity of the protein.

Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach in activin A, which is a member of the TGF-beta family, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular). Given the interaction between the undisclosed peptide and the

VEGFR-3 has not been characterized, it would require undue experimentation to determine how to make, and which of the possible peptides would be useful for treating which disease.

C. Enablement is not commensurate in scope with the claims as how the make and use any peptide with an amino acid sequence consisting of 7-100 amino acids, wherein the amino acid sequence includes amino acids satisfying the formula $GYWX_1X_2X_3W$ (SEQ ID NO: 67) or $GYWX_1X_2X_3WX_4$ wherein X_1, X_2, X_3 and/or X_4 comprises any amino acids and wherein the peptide binds humanVEGFR-3.

In order to make and use of the claimed invention, one has to be in possession of the peptide sequence and be able to binds human VEGFR-3.

In addition to the lack of guidance as to the rest of the 92 or 93 amino acids in the claimed peptide with an amino acid sequence consisting of 8-100 or 7-100 amino acids in length, there is insufficient guidance as to which amino acids to be substitute at position X_1, X_2, X_3 and/or X_4. Further, the term "includes" as defined in the specification is meant to be open-ended. It expands the undisclosed amino acids to include additional amino acids at either or both ends. There is a lack of guidance as to such amino acids to be added to either or both ends of $GYWX_1X_2X_3W$ (SEQ ID NO: 67) or $GYWX_1X_2X_3WX_4$. There are no working examples of such peptide binds to human VEGFR-3, in turn, could treat any disease. Further, the specification discloses cysteine residues are added at the N and Carboxy-terminal end of the formula, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 7-100 amino acids or 8-100 amino acids as now claimed.

With respect to claim 30, in addition to the issues in claims 1 and 21 discussed above, the "therapeutic protein amino acid sequence" attached to the amino acid sequence of the peptide in the claimed chimeric protein is not enabled. This is because a therapeutic protein without the amino acid sequence has no structure, much less function.

With respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not enabled for the reasons stated above. Further, there is insufficient guidance as to the binding specificity of the antibody or which "fragment thereof" other than Fc fragment of the antibody is part of the chimeric protein.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not teach modifying which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added and/or combination thereof such that the modified peptide increases in vivo half-life. With respect to the argument that glycosylation, pegylation are disclosed in the specification, the claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to claims 35-36, claims 1 and 21 are not enabled for the reasons stated above. Further, there is a lack of guidance as to the structure of any peptide heterodimer and/or any peptide homodimer comprising any combination of any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X1 through X8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8 and/or any first and second monomer peptides with an amino acid sequence consisting of 7-100 amino acids wherein the amino acid includes amino acids satisfying the formula $GYWX_1X_2X_3WX_4$ wherein X_1, X_2, X_3 and/or X_4 comprises any amino acids and wherein the peptide dimer maintains its secondary and tertiary structure and still binds specifically to humanVEGFR-3. Given the numerous combination and subscombination of peptide dimers mentioned above, there is insufficient working example showing any peptide dimer still binds to human VEGFR-3, much less for treating any disease.

Since the structure of the peptide in claims 1 and 21 above not enabled, it follows that any peptide further comprises any label such as a radionuclide, a dye, an enzyme, an enzyme

substrate (claim 75), any tumor necrosis factor (claim 31), any antibody or any fragment thereof (claim 32), any cytotoxic agent (claim 27), any radioisotope (claim 28), any anti-neoplastic prodrug (claim 29) and/or any therapeutic protein (claim 30) is not enabled. It also follows that any composition comprising any peptide mentioned above and a pharmaceutical acceptable carrier are not enabled.

Until the structures of the undisclosed peptides mentioned above that bind to human VEGFR-3 have been identified, the specification merely extends an invitation to one skill to come up with the structure of the claimed peptide. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/28/06 have been fully considered but are not found persuasive.

Applicants' position is that the claims are directed to a peptide of 8-100 amino acids, wherein the peptide includes a particular sequence of amino acids recited in the claims. Applicants have fully enabled a worker of ordinary skill in the art to make and use a peptide of 8-100 amino acids comprising the claimed shorter peptides. For example, the specification at page 35, line 8, to page 38, line 6, teaches methods for making peptides of varying lengths using techniques common in the art such as solid phase synthesis, preparation from a phage library, and recombinant expression systems. The specification indicates that a worker of ordinary skill can prepare a phage display library having peptides of a desired length range, e.g., from 4 to about 80 amino acids (Koivunen et al., J Nucl. Med. 40:883-88, 1999; Heiskanen et al., Virology. 262:321-32, 1999, abstracts included), and also teaches that the peptide may be a part of a fusion protein or a chimeric protein, e.g. a GST fusion protein (see page 38). It is irrelevant that the claims do

not recite a fusion protein such as GST as the Examiner contends, a worker of ordinary skill would understand from the disclosure in the specification that fusion proteins of any type are contemplated and guidance is provided in the specification for making such fusion proteins. This clearly teaches that a peptide of 8-100 amino acids in length is not out of reach of the ordinary worker. In the present application, the claims of the application are directed to a limited genus of peptides with specified amino acid length that bind to a specific cell receptor. The specification fully discloses methods to make the claimed peptides and methods to determine their binding specificity with respect to VEGFR-3. Similar to Wands, the invention provides a composition that binds to a specific binding target, with the binding identified using well-known screening methods. The present specification teaches methods to make the invention (e.g., peptide synthesis, phage display, other methods well-known in the art) and methods to screen the invention (e.g., VEGFR-3 binding assays), thereby providing ample guidance and direction to a worker of ordinary skill in the art. The peptides of the invention require a specific sequence or limited (conservative substitution) variants within that sequence. Additionally, the peptide sequence is of a finite length, e.g., 100 or 25 amino acid maximum length, such that a limited number of peptides are available and the binding domain of the claimed peptide is short compared to other proteins or peptides. Therefore, making the peptide of the present invention and screening for activity are performed relatively quickly using routine techniques, and the total number of combinations is orders of magnitude smaller than where a large protein of complex structure is contemplated.

In response to the argument that the specification indicates that a worker of ordinary skill can prepare a phage display library having peptides of a desired length range, e.g., from 4 to about 80 amino acids (Koivunen et al., J Nucl. Med. 40:883-88, 1999; Heiskanen et al., Virology. 262:321- 32, 1999, abstracts included), these identification of binding activity, once a peptide has been made, is not sufficient provide enablement for how to make. The specification discloses how to test for binding to VEGFR-3 using phage display library, these merely the sought-after activity, without any direction as how to make any peptide variants with amino acid sequence consisting of 8-100 or 7-100 amino acids in length having these activity. Further, none of the peptides identified using the phage-display libraries disclosed in the specification as filed are longer than 12 or 13 amino acids in length. Without the amino acid sequence, one of skill in the

art cannot make, let alone using the claimed invention for detecting, binding, diagnosing, and/or treating cancer expressing VEGFR-3.

With respect to the argument that the peptides of the invention require a specific sequence or limited (conservative substitution) variants within that sequence, there is no showing of any peptide with conservative substitution in the core peptide (formula) such that it maintains its three dimensional structure and still binds specifically to human VEGFR-3. There is no showing of any peptide longer than 13 amino acids in length that includes the core sequence with 3 or 4 conservative amino acid substitutions such that the peptide still binds specifically to human VEGFR-3, let alone a peptide with 7-100 or 8-100 amino acids in length.

A peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity to GYWLTIWG. A peptide of 8 amino acids in length with 4 amino acid conservative substitutions is 50% sequence identity to GYWLTIWG (claim 22). A peptide of 100 amino acids in length that includes GYWLTIWG formula with 3 additional amino acid substitutions in the formula is merely 5% sequence identity to GYWLTIWG. As such, 95 amino acids out of the 100 amino acids in the claimed peptide are not enabled, let alone the undisclosed peptide still binds to human VEGFR-3 for any purpose. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is clearly not enabled. The same reasoning applies to claim 3. Further, it is noted none of the peptides disclosed in Table 1 fits the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three or four conservative substitutions such as the ones recited in claim 4 at position X1 through X8 and still binds to human VEGFR-3. Since the amino acid sequence determines its function, predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acid(s) in the amino acid sequence, if any are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness.

However, the problem of predicting functional aspects of the product from mere sequence data of a single amino acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the peptides which can be made and used

having the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Again, the amino acid sequence itself is required for making the peptide. Screening for binding activity, once the peptide variant is made, is not sufficient guidance as how to make but only how to test for binding activity. As such, the specification merely extends an invitation to one skill in the art to come up with the structure of the claimed peptide with amino acid sequence consisting of 8-100 or 7-100 in length wherein the amino acid sequence includes the core sequence GYWLTIWG having no more than three or four conservative substitutions in the core sequence by screening whether it binds to VEGFR-3, and then test whether it would be useful for treating cancer. Even assuming the binding activity is conferred by the core sequence X1 through X8, it is also noted that none of the peptides shown in Table 1 demonstrates the claimed no more than three or four "conservative amino acid substitutions" within the core sequence at position X1 through X8 and maintains binding to human VEGFR-3. Finally, there is not a single peptide that is more than 13 amino acids in length such as 100 amino acids in length in the specification as filed and the peptide binds specifically to human VEGFR-3 other than the natural ligand VEGF-C or VEGF-D.

With regard to the cysteine deletion-substitution performed by Mason is not relevant to claim 1, because $X_1X_2X_3X_4X_5X_6X_7X_8$ are not cysteines, Mason et al is relevant to peptide dimer and cyclic peptide formation since both involve cysteine residues. The specification discloses two cysteine residues at the N and C-terminal ends of the core peptide to form a cyclic peptide with a defined Ig loop structure, see Table 1 in specification.

6. Claims 1-4, 12-13, 21-33, 35-36, 38 and 75-76 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any peptide with an amino acid sequence consisting of 8-100 or 8-25 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is

a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8, (2) any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8 further comprising amino- and carboxy-terminal cysteine residues, (3) any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence satisfied the formula: C $X_1X_2X_3X_4X_5X_6X_7X_8$C (SEQ ID NO: 33), (4) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X_1 through X_8 are any combination of amino acid residues, wherein the amino acid residue at X_1 is a selected from the group consisting of glycine, isoleucine, valine, leucine, praline, and norleucine, the amino acid residue at X_2 is a selected from the group consisting of tyrosine, serine, threonine, phenylalanine, and tryptophan, the amino acid residue at X_3 is selected from the group consisting of tryptophan, phenylalanine, and tyrosine, the amino acid residue at X_4 is a leucine, isoleucine, valine, alanine, glycine, phenylalanine, praline, norleucine, and

methionine, the amino acid residue at X_5 is a threonine, asparagines, glutamine, and serine, the amino acid residue at X_6 is a isoleucine, valine, leucine, alanine, glycine, phenylalanine, proline, norleucine, and methionine, the amino acid residue at X_7 is a tryptophan, phenylalanine, and tyrosine, and the amino acid residue at X_8 is a glycine, isoleucine, valine, leucine, alanine, proline, and norleucine and wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8, (5) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 comprising the sequence Y1GWLTIWGY2 (SEQ ID NO: 34), wherein Y1 and Y2 are amino acids, (6) any isolated peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and comprises the sequence CGYWLTIWGC (SEQ ID NO: 35), (7) any isolated peptide with an amino acid sequence consisting of 7-100 or 8-25 amino acids wherein the amino acid sequence includes amino acids satisfying the formula GYW $X_1X_2X_3$W (SEQ ID NO: 67), wherein X_1X_2 and X_3 comprise any amino acids and wherein the peptide binds human VEGFR-3, (8) any isolated peptide with an amino acid sequence consisting of 7-100 amino acids wherein the amino acid sequence satisfying the formula GYW $X_1X_2X_3WX_4$ (SEQ ID NO: 68), wherein $X_1X_2X_3$ and X_4 comprises any amino acids and wherein the peptide binds human VEGFR-3, (9) any isolated peptide mentioned above further comprising amino- and carboxy-terminal cysteine residues, (10) any isolated peptide mentioned above wherein said peptide further comprises an intramolecular bond between any amino acid residues to form a cyclic peptide, (11) any isolated peptide mentioned above wherein the peptide comprises amino- and carboxyl-terminal cysteines, and the intramolecular bond comprises a disulfide bond between the cysteines, (12) any isolated peptide mentioned above further comprising any cytotoxic agent such as radioisotope or any anti-neoplastic pro-drug, any label such as any radionuclide, any dye, any enzyme, or any enzyme substrate attached to the peptide, (13) any chimeric protein as set forth in claims 30-31, (14) any peptide mentioned above attached to any antibody or any fragment thereof, (15) any peptide mentioned above wherein the peptide further comprises any modification to increase the circulating *in-vivo* half-life of the peptide in any mammal, (16) any peptide dimer comprising any first and second peptides mentioned above as set forth in claims 35-36 and (17) any composition comprising any isolated peptide mentioned above in a pharmaceutically acceptable carrier.

The specification discloses only isolated peptide selected from the group consisting of CGYWLTIWGC (SEQ ID NO: 35), SGYWWDTWF (SEQ ID N0: 36), SCYWRDTWF (SEQ

ID NO: 37), KVGWSSPDW (SEQ ID N0: 38), FVGWTKVLG (SEQ ID N0: 39), YSSSMRWRH (SEQ ID N0: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID N0: 42), WFSASLRFR (SEQ ID NO: 43), or the peptides shown in Table 1 at page 27 wherein the peptide binds to human VEGFR-3 (pages 16, and 27). The said peptide GYWLTIWG further comprises amino and carboxy terminal cysteine residues to form a cyclic peptide via an intramolecular bond between said cysteine residues. The specification further discloses a peptide dimer comprising a first and second peptide wherein the first and second peptides are the same SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or detection assays.

With the exception of the specific peptide mentioned above that binds to human VEGFR-3, there is insufficient written description about the structure of any peptide as set forth in claims 1-4, 12-13, 21-33, 35-36, 38 and 75-76. This is because a peptide with 8-100 or 7-100 amino acids in length without the amino acid sequence has no structure, much less function. Further, there is not a single peptide that is over 12 amino acids in length and binds to human VEGFR-3 in the specification as filed. As such, the rest of the 92 or 93 amino acids in the formula as set forth in claims 1 and 21 are not adequately described. For the sake of illustration, assuming a peptide that is 100 amino acids in length and has 3 specified conservative amino acids substitution in the formula, this is equivalent to a peptide with 97 amino acids out of the 100 amino acid residues that are not adequately described. The term "includes" or "including" as defined by the specification to mean "comprising", which is open-ended. There is inadequate written description about the amino acids to be added. There is no disclosure of any peptide longer than 12 amino acids in length such as 100 amino acids in length that retains its three dimensional structure and binds to human VEGFR-3. Further, there is inadequate written description about which three amino acids to be substitute for which amino acids within the X1 through X8 in a peptide with 8-100 amino acids in length.

Even assuming the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ in the peptide with 8-100 amino acids in length is the "core sequence" or the common attribute for binding to human VEGFR-3 wherein the amino acid residue at X_1 is a glycine residue, the amino acid residue at X_2 is a tyrosine residue, the amino acid residue at X_3 is a tryptophan residue, the amino acid residue at X_4 is a leucine residue, the amino acid residue at X_5 is a threonine, the amino acid residue at X_6 is a isoleucine, the amino acid residue at X_7 is a tryptophan, and the amino acid residue at X_8 is a glycine, the specification does not teach which combination of any 3 conserved amino acid

substitution at position X_1 through X_8 retains binding specificity to the human VEGFR-3. A peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity to GYWLTIWG. A peptide of 100 amino acids in length that includes GYWLTIWG formula with 3 additional amino acid substitutions in said formula is merely 5% sequence identity to GYWLTIWG. As such, 95 amino acids out of the 100 amino acids in the claimed peptide are not adequately described. Any peptide with an amino acid sequence consisting of 8-100 amino acids in length having any 3 amino acid substations in $X_1X_2X_3X_4X_5X_6X_7X_8$ that has no resemblance to CGYWLTIWGC is clearly not adequately described. The same reasoning applies to claim 3. Further, it is noted none of the peptides disclosed in Table 1 fits the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three conservative substitutions such as the ones recited in claim 4 at position X1 through X8 and still binds to human VEGFR-3. As such, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 8-100 in length that includes eight amino acids satisfying the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three conservative substitutions and binds to human VEGFR-3. Thus applicants are not in possession of such peptide.

Further, the specification discloses the cysteine residues are added at the N and Carboxy-terminal end of the formula $X_1X_2X_3X_4X_5X_6X_7X_8$, not at the N and C-terminal ends of the isolated peptide with an amino acid sequence consisting of 100, 99, 98…25 etc amino acids in length.

With regard to claim 4, although the specific conservative amino acids substitution are recited in the claim, there is inadequate written description about which three amino acid residues in $X_1X_2X_3X_4X_5X_6X_7X_8$ in a peptide of 8-100 amino acids in length to be substituted such that it maintains its conformation and binding specificity. Even assuming the $X_1X_2X_3X_4X_5X_6X_7X_8$ are adequate described, the rest of the 92 amino acids are not adequately described without the amino acid sequence.

With regard to claim 12, the specification discloses Y1 and Y2 are cysteine. The specification does not adequate describe any with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to any VEGFR-3 and wherein the amino acid sequence includes Y1GYWLTIWGY2 (SEQ ID NO: 34) wherein Y1 and Y2 are any amino acids. This is because there are no disclosures of other amino acids at Y1 and Y2 could form cyclic peptide and still binds to human VEGFR-3. The term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is a lack of disclosure about the amino acids to be added to $Y_1GYWLTIWGY_2$.

With regard to claim 13, since the formula peptide GGYWLTIWGC (SEQ ID NO: 35) is within the amino acid sequence consisting of 8-100 amino acids in length, the rest of the 90 amino acids are not adequately described without the amino acid sequence. There is a lack of disclosure about the amino acids to be added to either or both ends of CGYWLTIWGC such that the peptide maintains its conformation and binds specifically to human VEGFR-3. The same reasoning applies to claims 21-29.

With respect to claim 30, in addition to the issues in claims 1 and 21 discussed above, the fusion partner such as "the therapeutic *amino acid sequence*" attached to the peptide mentioned above is not adequate described without the amino acid sequence of the therapeutic protein.

With respect to claims 31, although the fusion partner tumor necrosis factor is recited claim 31, claim 31 depends from claims 1 or 21. Claims 1 and 21 are not adequately described for the reasons stated above.

With respect to claims 32, although the fusion partner antibody or fragment thereof is recited claim 32, claim 32 depends from claims 1 or 21. Claims 1 and 21 are not adequately described for the reasons stated above. Further, there is inadequate disclosure about the binding specificity of the antibody and which fragment of the antibody is part of the claimed chimeric protein.

With respect to claim 33, the only modification to increase the circulating in-vivo half-life of the peptide as disclosed in the specification is to fuse the peptide to the Fc fragment of an antibody, not just any fragment of an antibody. The term "modification" encompasses any modification of an isolated peptide of claims 1 or 21. The specification does not disclose which amino acids within the peptide that has 8-100 amino acids in length is to be substituted, deleted, added and/or combination thereof such that the modified peptide increases in vivo half-life. The specification also discloses glycosylation, and pegylation. However, the claim does not recite the specific modification such as the peptide is glycosylated or pegylated.

With respect to claim 34, claim 34 recites a peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide monomer comprises "a" peptide according to any one of claims 1 or 21 and wherein the dimer binds to VEGFR-3. The claim encompasses any peptide dimer wherein one of the peptide monomer is from any fragment of a peptide from claims 1 or claim 21 and wherein the dimer binds to any VEGFR-3. Claims 1 and 21 are not adequately described for the reasons stated above. Assuming one of the monomers in the peptide dimer is from the peptide recited in claims 1 or 21, the structure of the other monomer in the

claimed peptide dimer is not adequately described. Further, the term "a peptide" instead of "the peptide" according claims 1 or 21 means any fragment of the peptide according to claims 1 or 21. There is no disclosure about which fragment such as one or two amino acids of the peptide according to claims 1 or 21 is useful for forming dimer and still binds to human VEGFR-3.

With respect to claims 35-36, claims 1 and 21 are not adequately described for the reasons stated above. The term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both ends. As such, the structures of the first and second peptide without the amino acid sequences that bind to any VEGFR-3 are not adequately described.

With respect to claim 37, claims 1 and 21 are not adequately described for the reasons stated above. Further, none of the peptides in the specification as filed has been shown to bind to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) other than human VEGFR-3. As such, any peptide that binds to any VEGFR-1, any VEGFR-2, any neuropilin-1 (NP-1) and any neutopilin-2 (NP-2) without the amino acid sequence is not adequately described.

With respect to claim 38, since the structure of peptide in claims 1 and claim 21 are not adequately described, it follows that any composition comprising such peptide and a pharmaceutical acceptable carrier is not described.

The specification discloses only peptides that are 10 amino acids in length and binds only human VEGFR-3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 8-100 or 7-100 amino acids in length that bind to human VEGFR-3 to describe the genus for the claimed peptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/28/06 have been fully considered but are not found persuasive.

Applicants' position is that the specification described several genera of peptides, including peptides of 7-100 amino acids and how to make such peptides, see specification at pp.

14-41. Focusing on the genus of peptides defined by $X_1X_2X_3X_4X_5X_6X_7X_8$ in claim 1, it is clear that the claim scope is quite small in relation to many chemical and biomolecule claims routinely allowed by the Patent Office. Each of the eight positions in the formula in claim 1 is defined by a single amino acid residue, and the formula as a whole permits no more than three conservative amino acid substitutions relative to the specified amino acids. This genus defined by Applicants' core sequence and up to three conservative substitutions is, many orders of magnitude smaller than a typical polypeptide or polynucleotides genus defined, e.g., by a "95% identity" limitation relative to a much longer sequence. The PTO's own Written Description Training Materials, such as a 95% identity claim can be adequately described by a single disclosed embodiment. The rejection is basing on the description of the optional additional structure, not required for function and not required by the claims. The application demonstrates that short peptides, such as the peptide CGYWLTIWGC, can bind VEGFR-3. It is well known that the natural ligands of VEGFR-3, including VEGF-C and VEGF-D, are longer than 100 amino acids. The application also describes how to make longer peptides that contain the core structure (the "necessary common attributes". Although claims 13 and 35 (amended) use the term "comprises/comprising", these claims depend from claims 1 or 21, and thus are properly interpreted to incorporate the 100 amino acid maximum recited in claim 1 or 21. The Patent Office wrongly asserts that the description of cysteines used in the invention is limited to cysteines at the ends of the 8-mer formula. Original claims 2 and 25 also provide written description support for a terminal cysteine embodiment, because the original claims form part of the written description. With respect to claims 30 and 32, adequate novelty lies in the VEGFR-3 binding peptide defined in the independent claims, and any not in the fusion partner. The core binding structure is the "necessary common attribute" relevant to written description of this invention. With respect to claim 33, the Examiner alleged that the only modification taught in the application for increasing in vivo circulating half life is an Fc fusion. This is incorrect. The application teaches, "Standard pharmaceutical and formulation chemistry is used to achieve such goals, e.g., through glycosylation, pegylation, introduction of non-hydrolyzable bonds, mixing with pharmaceutically acceptable diluents, adjuvants, or carriers, and the like." Additional description of half-life increasing modifications are found, e.g., at pages 32-34. Claim 33 represents yet another example of a dependent claim for which a brief description suffices in view of the skill of those in the art. The Examiner's concern that the claim encompasses any

modification is misplaced, because the claim only encompasses modification that increases half-life, and would be interpreted in the context of the application.

In response to the claim scope is quite small in relation to many chemical and biomolecule claims routinely allowed by the Patent Office, every case is examined on its own merit. In the instant case, the claims encompass any peptide 8-100 amino acids in length merely having 5 amino acids identical to the formula or the "core sequence" GYWLTIWG. Even assuming the claimed peptide is 8 amino acids in length, a peptide of 8 amino acids in length with 3 amino acid conservative substitutions is 63% sequence identity. A peptide of 100 amino acids in length that includes GYWLTIWG formula with no more than three additional amino acid substitutions in said formula is merely 5% sequence identity to GYWLTIWG, let alone the undisclosed peptide still maintains its conformation (discontinuous epitope) and binds to human VEGFR-3. Clearly, a peptide with 63% sequence identity to GYWLTIWG or a peptide with 5% sequence identity is far below the "95% sequence identity" as pointed out by Applicants in the PTO's own Written Description requirement.

With respect to the argument that the rejection is not basing on the core sequence, the specification does not teach which combination of three amino acids substitution within GYWLTIWG or X1 through X8 that it still maintains its conformation and binds specifically to human VEGFR-3. The specification at page 28 discloses GYWLTIWG peptide mimicked a *discontinuous binding site* and sequence alignment of claimed genus peptides such as the ones shown in Table 1 have no consensus motifs with VEGF-C, the natural ligand for human VEGFR-3. It is also noted that none of the peptides shown in Table 1 fits the claimed no more than three "conservative amino acid substitutions" within the core sequence at position X1 through X8 in a peptide that is up to 100 amino acids in length. There is not a single peptide that is more than 13 amino acids in length in the specification as filed and binds specifically to human VEGFR-3 other than the natural ligand VEGF-C or VEGF-D. As such, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with an amino acid sequence consisting of 8-100 in length that includes eight amino acids satisfying the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ having any three conservative substitutions and binds to human VEGFR-3.

In contrast to applicants' assertion that the specification describes how to make longer peptides that contain the core structure, in order to make or synthesize a peptide, the amino acid sequence itself is required. The specification does not describe any peptides longer than the core

structure without the amino acid sequence, especially the therapeutic protein amino acid sequence attached to the core sequence. Let alone how to make! Although the specification discloses how to screen for peptide that binds to human VEGFR-3, screening once the peptide variant is made, is not how to make.

With respect to claim 13, there is not a single peptide that is more than 13 amino acids in length comprises the core sequence in the specification as filed and binds specifically to human VEGFR-3 other than the natural ligand VEGF-C or VEGF-D.

With respect to claim 35, claims 1 and 21 are not adequately described for the reasons stated above. Further, there is insufficient written description about the structure of any peptide heterodimer and/or any peptide homodimer comprising any combination of any peptide with an amino acid sequence consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X1 through X8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8 and/or any first and second monomer peptides with an amino acid sequence consisting of 7-100 amino acids wherein the amino acid includes amino acids satisfying the formula $GYWX_1X_2X_3WX_4$ wherein X_1, X_2, X_3 and/or X_4 comprises any amino acids and wherein the peptide dimer maintains its secondary and/or tertiary structure and still binds specifically to humanVEGFR-3. Given the numerous combination and subscombination of peptide dimers mentioned above, any peptide dimer comprising any first and any second peptide mentioned above and still binds to human VEGFR-3 is not adequately described.

With respect to the argument that original claims 2 and 25 also provide written description support for a terminal cysteine embodiment at the end of the 8-100 amino acids instead of cysteines at the ends of the 8-mer formula because the original claims form part of the

written description, the specification must provide antecedent basis for any claims, including original claims. Further, the specification at page 28 and peptides in Table 1 disclose the cysteine residues are at the end of the 8-mer formula. The specification and the sequence listing as filed do not describe any peptide up to 100 amino acids in length with cysteine residues at the ends of the 100-mer peptide and still maintains its conformation and binds to human VEGFR-3.

With respect to argument that adequate novelty in claims 30 and 32 lies in the VEGFR-3 binding peptide defined in the independent claims, and not in the fusion partner, the specification does not teach which combination of three amino acids substitution within GYWLTIWG or X1 through X8 that it still binds specifically to human VEGFR-3. The specification at page 28 discloses GYWLTIWG peptide mimicked a *discontinuous binding site* and sequence alignment of claimed genus peptides such as the ones shown in Table 1 have no consensus motifs with VEGF-C, the natural ligand for human VEGFR-3. It is also noted that none of the peptides shown in Table 1 fits the claimed no more than three "conservative amino acid substitutions" within the core sequence at position X1 through X8 in a peptide that is up to 100 amino acids in length. There is not a single peptide that is more than 13 amino acids in length in the specification as filed and binds specifically to human VEGFR-3 other than the natural ligand VEGF-C or VEGF-D. Further, claim 30 recites a chimeric protein comprising a "therapeutic protein amino acid sequence" attached to the amino acid sequence of a peptide consisting of 8-100 amino acids, wherein the peptide binds to human VEGFR-3 and wherein the amino acid sequence includes $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32), wherein X1 through X8 are amino acid residues, wherein the amino acid residue at X_1 is a glycine residue or any conservative substitution thereof, the amino acid residue at X_2 is a tyrosine residue or any conservative substitution thereof, the amino acid residue at X_3 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_4 is a leucine residue or any conservative substitution thereof, the amino acid residue at X_5 is a threonine residue or any conservative substitution thereof, the amino acid residue at X_6 is a isoleucine residue or any conservative substitution thereof, the amino acid residue at X_7 is a tryptophan residue or any conservative substitution thereof, the amino acid residue at X_8 is a glycine residue or any conservative substitution thereof, wherein the peptide comprises no more than any 3 conserved amino acid substitution at position X_1 through X_8 or any peptide with an amino acid sequence consisting of 7-100 amino acids wherein the amino acid includes amino acids satisfying the formula $GYWX_1X_2X_3WX_4$ wherein X_1, X_2, X_3 and/or X_4 comprises any amino acids. Not only the

"amino acid sequence" of any and all therapeutic protein in the chimeric protein is not adequately described, the specific combination of which three conservative amino acids in the core sequence of a peptide up to 100 amino acids in length is not adequately described, let alone the rest of the 92 amino acids in the peptide and whether such as chimeric protein still binds to human VEGFR-3.

With respect to claim 33 that the specification teaches modification to increase the circulating in-vivo half-life of the peptide, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The modification in claim 33 encompasses any modification to the peptide, and not limited to what is disclosed in the specification. The specification does not teach which modification to the peptide, especially the core sequence to increase the circulating half-life of the peptide.

7. Claims 2 and 23 stand rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "isolated peptide with an amino acid sequence consisting of 8-100 amino acids ...further comprising amino- and carboxy-terminal cysteine residues" in claim 2 represents a departure from the specification and the claims as originally filed. The specification at page 15 discloses the cysteine residues are located at the amino- and carboxy-terminal of formula $CX_1X_2X_3X_4X_5X_6X_7X_8C$ to form a cyclic peptide. The claim as written, the cysteine residues are located at the amino- and carboxy-terminal of a peptide consisting of 100, 99, 98...13 amino acids in length.

The "isolated peptide with an amino acid sequence consisting of 7-100 amino acids ...further comprising amino- and carboxy-terminal cysteine residues" in claim 23, represents a departure from the specification and the claims as originally filed. The specification at page 17 discloses the cysteine residues are located at the amino- and carboxy-terminal of the peptide $GYWX_1X_2X_3WX_4$ to form a cyclic peptide.

Applicants' arguments filed 11/28/06 have been fully considered but are not found persuasive.

Applicants' position is that original claims 2 and 23 and paragraph bridging pages 14-15 of the specification provide formula for some preferred variations of the invention. The teaching of the specific embodiments does not negate the more general teaching that peptides up to 100 amino acids with terminal cysteines, are part of the invention.

In response, the specification at page 28 and the peptides in Table 1 clearly disclose the cysteine residues are located at the N and C-terminal of the formula $CX_1X_2X_3X_4X_5X_6X_7X_8C$ or CGYWLTIWGC. The specification and the sequence listing as filed do not describe a peptide with any length such as 100, 99, 97....13 amino acids in length and comprising N and C-terminal cysteines residues.

8. The following new ground of rejection is necessitated by the amendment filed11/28/06.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "monomers" in claim 36 has no antecedent basis in base claim 35 because the word "monomers" has been deleted in claim 35.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 16, 2007

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